IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	10/084,674	Confirmation No. :	2545
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Filed	:	February 28, 2002		
TC/A.U.	:	1618		
Examiner	:	Simon J. Oh		
Docket No.	:	029310.50986		
Customer No.	:	23911		
Title	:	Oral Dosage Forms		

PRE-APPEAL BRIEF REQUEST FOR REVIEW

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Sir:

The presently claimed invention relates to oral dosage forms with controlled total-release of an active substance, wherein the same active substance is present in the form of at least two different salts which are present in the dosage form in a solid aggregation state and which have different in-vitro release rates of the active substance.

Administration of an active substance in the form of preparations, from which this active substance is released in a controlled manner, is advantageous for many therapies. For example, the controlled release of an active substance with a relatively short half-life will prolong its availability in the body. Moreover, uniform blood levels can be adjusted in this manner; any undesirable accompanying symptoms may, optionally, be minimized; and observance of dosage specifications can be improved.

Conventionally, the controlled release of an active substance from oral dosage forms can be achieved only through relatively expensive formulation procedures, such as coating the oral dosage forms containing active substances with a retarding film coating or embedding the active substances in a retarding matrix. If a different release of partial quantities of an active substance is required in order to control the overall release profile, the same active substance or the same active-substance salt may be processed separately to provide different formulations, which may then be combined, for example, as a retarded and a non-retarded form of one dosage form.

The present invention, in contrast, is able to provide oral dosage forms of an active substance from which this active substance is released in a controlled manner without the need for expensive, separate formulation stages to adjust the overall release

profile of the active substance from a dosage form. This is achieved by providing oral dosage forms in which the same active substance is present in the form of at least two different salts, which are present in the dosage form in the solid aggregation state and which have a different in-vitro release of this active substance. The oral dosage forms according to the invention have the advantage that the active substance can be released in a controlled manner in accordance with the desired total-release profile, e.g. in a pulsed or multi-phase manner over the given period, without the need for expensive, separate formulation stages for the active substance. This means that the time and therefore also the cost for the manufacture of the oral dosage forms according to the invention can be minimized.

Thus, the presently claimed invention is a controlled-release oral dosage formulation of a salt-forming active ingredient, wherein:

(1) the active ingredient is present as at least two different salts in a solid aggregation state from which the active ingredient is released by dissolution of said salts,

(2) the two different salts have different water solubilities and release the active ingredient *in-vitro* at different release rates, and

(3) the water solubilities of the at least two different salts differ from one another at least by a factor of 2.

Oral dosage formulations are excluded which comprise a resin carrying a sulfonate group and a resin carrying a carboxyl group and which contain an active ingredient in a form fixed to these resins.

Applicants have found that controlled release of an active substance from an oral dosage form can simply be achieved in an entirely new way by combining two or more different salts of the same active substance having different water solubilities in a common dosage form from which the active ingredient is released by dissolution of the salts. As demonstrated in the examples of the application, this simple and elegant principle makes it possible to achieve controlled or sustained release of an active ingredient in relatively simple and consequently relatively inexpensive formulations.

Applicants submit that the rejection of claims 1, 3-9, 11, 12, 15, 17, 18, 21, 30-32, 55-58 and 62-67 under 35 U.S.C. §103(a) over Oshlack, *et al.*, WO 99/01111 (hereinafter "Oshlack"), is in error.

Oshlack discloses oral sustained release solid dosage forms of tramadol having extended release over at least 24 hours. Controlled release from these dosage forms is

achieved via the use of a matrix of a hydrophobic material and elaborate formulation steps, e.g., curing within a certain temperature range.

However, it was exactly the object of the present invention to provide oral dosage forms of an active substance that allow for controlled release of the active substance without the need for using elaborate separate formulation steps to adjust the release profile of the active substance.

There is not the slightest hint in Oshlack that controlled release of an active substance could be achieved without the use of certain controlled release agents such as hydrophobic materials or certain formulation measures, such as curing within a certain temperature range. In particular, there is no hint that controlled release from oral dosage forms can simply be achieved by combining two or more different salts of one and the same active substance, thereby adjusting a desired release or liberation profile of the active substance as claimed in the present application without elaborate formulation steps.

Indeed, the record contains nothing to show that it is known to adjust the release profile of an active substance by selecting active substance salts of varying solubility, much less any evidence to suggest that the release profile of an active substance could be controlled by using a mixture of at least two different salts of one and the same active agent having solubilities which differ by a factor of at least two, as claimed by Applicants. Rather, the approach of the prior art, as demonstrated by Oshlack, has been to control the release of an active agent by varying the coatings or encapsulating agents. In other words, the art teaches controlling the release profile by varying the formulation of the vehicle for delivering the active agent, and not by the novel approach of using two salts of the same active agent having different solubilities.

The Examiner concludes, however, without any support that it is known to influence the release profile of an active agent by varying the characteristics (including solubility) of polymer vehicles used for delivering the active agent, and that "it is well within the purview of one of ordinary skill in the art to influence the release of an active agent by using different forms of the same active agent that exhibit different solubility characteristics" (Final Action, page 4, second paragraph). As pointed out by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 SCt 1727, 82 USPQ2d 1385, 1396 (U.S. 2007), such unsupported conclusory statements cannot sustain a rejection.

> [R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness". (Quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329 (Fed. Cir. 2006) with approval).

Although an explicit teaching, suggestion or motivation need not be found in the cited references, to properly reject for obviousness, it is nevertheless necessary for the Examiner to articulate a convincing rationale as to what would lead a person skilled in the art to depart from the teachings of the prior art and strike out in the new direction claimed by applicants as their invention. This the Examiner has failed to do, and this failure constitutes a clear error in the rejection. It follows that a proper, *prima facie* case of obviousness has not been made out, and the rejection should be withdrawn.

Moreover, the statement of rejection makes no attempt whatever to explain how one skilled in the art would arrive at the claim requirement that the solubilities of the at least two salts differ by a factor of at least 2.

The Examiner's reliance on old CCPA decisions holding it *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, is misplaced. However true this may be regarding mixtures of two different pharmaceutically active agents, the logic breaks down and is not applicable to mixtures of two different salts of the same active agent as claimed in the present invention. These old cases dealing with mixtures of different active agents known to be useful for the same purpose are inapposite because their facts are different. Two different active agents can be presumed to have some differences in activity so that the combination of the two could be expected to yield a broadened spectrum of activity. The same is **not** true for two different salts of the same active ingredient. Consequently, the reasoning of cases dealing with combinations of two different active agents is not applicable to the present invention, which deals with a combination of at least two different salts of the same active agent having different solubilities. The record is devoid of any example of such a mixture, and with good reason. The formation of a mixture of two different salts of the same active ingredient is unquestionably more troublesome and inconvenient than the provision of a single salt. There is nothing that would lead a person of skill in the art to expect any advantage from using a mixture of two materials over using a single material when there is only one active ingredient present in the mixture. All that the prior art would lead a person of ordinary skill in the

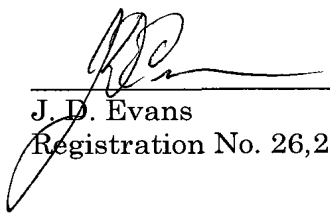
art to expect would be that such a mixture of salts of the same active ingredient would have the same effect as a single salt of the active ingredient. Thus, there is no reason why one of ordinary skill should seek to form such a mixture of salts of the same active ingredient having different solubilities, and it cannot fairly be said to be obvious for a person of ordinary skill to incur the trouble and inconvenience of forming such a mixture for no reason.

It is only the Applicants who have recognized that unexpected advantages of extended activity could be attained from using a mixture of at least two different salts of the same active ingredient having different solubilities as claimed in the present invention. Consequently, it is only after a consideration of the Applicant's disclosure that there is any reason or motivation to form such a mixture. However, such hindsight consideration is clearly improper.

Obviousness is not susceptible of determination by rote application of mechanical rules derived from cases with different facts. Rather, obviousness in any given case must be decided on the facts of that case. *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992) ("Every case, particularly those raising the issue of obviousness under section 103, must necessarily be decided upon its own facts.") Under the facts of this case, since there is no reason to make a combination of at least two different salts of the same active ingredient having different solubilities as claimed, the obviousness rejection is not well founded. Thus, Applicants respectfully submit that their presently claimed invention is not obvious in view of Oshlack, and withdrawal of the rejection is respectfully requested.

Respectfully submitted,

December 11, 2007



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